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Title of the Invention: A Stomach and Intestinal Medicine Active Against *Helicobacter Pylori*

Abstract

Problem There is a strong desire for the development of a stomach and intestinal medicine which is effective for the prevention or treatment of stomach and intestinal disorders such as gastritis, stomach ulcers and duodenal ulcers caused by *helicobacter pylori* infection, which has a stronger activity against *helicobacter pylori* and contains safe drug components.

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Means of Solution A stomach and intestinal medicine that combines (1) natural drug powder or extract components of goldthread and/or oubaku and (2) natural drug powder or extract components of dried orange peel and that is active against *helicobacter pylori*.

Scope of Patent Claims

Claim 1 A stomach and intestinal medicine that combines (1) natural drug powder or extract components of goldthread and/or oubaku and (2) natural drug powder or extract components of dried orange peel and that is active against *helicobacter pylori.*

Claim 2 The stomach and intestinal medicine disclosed in Claim 1 that uses about 2~200 parts by weight (ppw), when converted to the primary drug, of natural drug powder or extract components of dried orange peel (2) to 1ppw, when converted to the primary drug, of natural drug powder or extract components of goldthread (1).

Claim 3 The stomach and intestinal medicine disclosed in Claim 1 that uses about 1~100ppw, when converted to the primary drug, of natural drug powder or extract components of dried orange peel (2) to 1ppw, when converted to the primary drug, of natural drug powder or extract components of oubaku (1).

Claim 4 The stomach and intestinal medicine disclosed in Claim 1 that uses about 1~200ppw, when converted to the primary drug, of natural drug powder or extract components of dried orange peel (2) to 1ppw, when converted to the primary drug, of natural drug powder or extract components of goldthread and oubaku.

Claim 5 The stomach and intestinal medicine disclosed in Claim 1 that is a prevention or treatment drug for stomach and intestinal disorders caused by *helicobacter pylori* infection.

Claim 6 The stomach and intestinal medicine disclosed in Claim 1 that contains at least one sort of histamine H_2 receptor antagonist, proton pump inhibitor, stomach mucous membrane protective type of gastritis and digestive ulcer treatment drug, antacid drug and diarrhoea prevention drug.

Claim 7 The stomach and intestinal medicine disclosed in Claim 1 which contains a histamine H_2 receptor antagonist.

Claim 8 The stomach and intestinal medicine disclosed in Claim 7 where the histamine H_2 receptor antagonist is cimetidine or a pharmacologically permissible salt of this.

Claim 9 The stomach and intestinal medicine disclosed in Claim 1 that contains an antacid drug.

Claim 10 A stomach and intestinal medicine consisting of (1) a natural drug powder or extract component of goldthread and/or oubaku and (2) natural drug powder or extract component of dried orange peel as its drug components.

Claim 11 The stomach and intestinal medicine disclosed in Claim 10 that contains at least one type of histamine H_2 receptor antagonist, proton pump inhibitor, stomach mucous membrane protective type of gastritis and digestive ulcer treatment drug, antacid drug and diarrhoea prevention drug.

Claim 12 A stomach and intestinal medicine that has activity against *helicobacter pylori* consisting of natural drug powder or extract components of goldthread, oubaku and dried orange peel.

Claim 13 A method of use of a natural drug powder or extract component of dried orange peel for strengthening the activity against *helicobacter pylori* of goldthread and/or oubaku.

Detailed Explanation of the Invention

0001

Technical Field to Which the Invention Belongs

This invention relates to a stomach and intestinal medicine that combines a natural drug powder or extract component of goldthread and/or oubaku and a natural drug powder or extract component of dried orange peel. This stomach and intestinal medicine is active against *helicobacter pylori* and is useful for the prevention, treatment and prevention of re-occurrence of such things as gastritis, stomach ulcers and duodenal ulcers.

0002

Prior Art

It is already known that some types of drugs show an anti-bacterial action. For example, an anti-bacterial agent against *helicobacter pylori* containing one type or more of natural drug powder or extract components of goldthread has been presented in Japanese Patent Publication Hei 8-295632. A medical composition containing (a) a natural drug powder or extract component active against *helicobacter pylori* and (b) at least one type of histamine H_2 receptor antagonist, proton pump inhibitor, stomach mucous membrane protective type of gastritis and digestive ulcer treatment drug, antacid drug and diarrhoea prevention drug has been described in Japanese Patent Publication Hei 10-109942 and goldthread and the like have been stated as the said drug. Administration of PPI or H_2 blocker and administration of a stomach powder as one of the subsequent herbal medicine treatments has been described in the right hand column of page 78 of the May 1996 summary of the lectures at the 47th Japan Oriental Medical Science General Meeting.

0003

Problems to Be Overcome by the Invention

As a method of treatment for eradicating *helicobacter pylori*, a combination of 3 types such as one type or more of penicillin system, cephalosporin system, tetracycline system, new quinolone system and macrolide system antibiotic and bismuth drugs and proton pump inhibitors (PPI) has been the mainstream, but, although antibiotics have a strong bactericidal effect, there are problems such as the side effects of hypersensitivity and the appearance of resistant bacteria. The development of a stomach and intestinal medicine is wanted which is effective for the prevention or treatment of stomach and intestinal disorders such as gastritis, stomach ulcers and duodenal ulcers caused by *helicobacter pylori* infection, which has a strong action against *helicobacter pylori* and which contains drug components that are extremely safe for the human body.

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Means of Overcoming the Problems

As the result of diligent study of the said problems, the inventors of this invention discovered that a combination of specific drugs exercised a multiplied inhibiting action on the propagation of *helicobacter pylori* bacteria. In addition, they discovered that, by combining histamine H_2 antagonists or proton pump inhibitors (for example, lansoprazole, rabeprazole and omeprazole), stomach mucous membrane protective types of gastritis and digestive ulcer treatment drugs, bismuth agents and, in addition, antacid drugs and the like that are generally used in the treatment of such things as gastritis and that were hitherto said to have very weak or no anti-bacterial activity against *helicobacter pylori*, they obtained an unexpectedly great effect in the prevention, treatment and prevention of re-occurrence of such things as gastritis, stomach ulcers and duodenal ulcers and they accomplished this invention. That is to say, this invention relates to

(1) a stomach and intestinal medicine that combines ① natural drug powder or extract components of goldthread and/or oubaku and ② natural drug powder or extract components of dried orange peel and that is active against *helicobacter pylori.*

(2) the stomach and intestinal medicine disclosed in the said (1) that uses ② about 2~200ppw, when converted to the primary drug, of natural drug powder or extract components of dried orange peel to ① 1ppw, when converted to the primary drug, of natural drug powder or extract components of goldthread,

(3) the stomach and intestinal medicine disclosed in the said (1) that uses ② about 1~100ppw, when converted to the primary drug, of natural drug powder or extract components of dried orange peel to ① 1ppw, when converted to the primary drug, of natural drug powder or extract components of oubaku,

(4) the stomach and intestinal medicine disclosed in the said (1) that uses ② about 1~200ppw, when converted to the primary drug, of natural drug powder or extract components of dried orange peel to ①1ppw, when converted to the primary drug, of natural drug powder or extract components of goldthread and oubaku,

(5) the stomach and intestinal medicine disclosed in the said (1) that is a prevention or treatment drug for stomach and intestinal disorders caused by *helicobacter pylori* infection.

(6) the stomach and intestinal medicine disclosed in the said (1) that contains at least one sort of histamine H_2 receptor antagonist, proton pump inhibitor, stomach mucous membrane protective type of gastritis and digestive ulcer treatment drug, antacid drug and diarrhoea prevention drug,

(7) the stomach and intestinal medicine disclosed in the said (1) which contains a histamine H_2 receptor antagonist,

(8) the stomach and intestinal medicine disclosed in the said (7) where the histamine H_2 receptor antagonist is cimetidine or a pharmacologically permissible salt of this,

(9) the stomach and intestinal medicine disclosed in the said (1) that contains an antacid drug,

(10) a stomach and intestinal medicine consisting of (1) a natural drug powder or extract component of goldthread and/or oubaku and (2) natural drug powder or extract component of dried orange peel as its drug components,

(11) The stomach and intestinal medicine disclosed in the said (10) that contains at least one type of histamine H_2 receptor antagonist, proton pump inhibitor, stomach mucous membrane protective type of gastritis and digestive ulcer treatment drug, antacid drug and diarrhoea prevention drug,

(12) a stomach and intestinal medicine that has activity against *helicobacter pylori* consisting of natural drug powder or extract components of goldthread, oubaku and dried orange peel,

(13) a method of use of natural drug powder or extract components of dried orange peel for strengthening the activity against *helicobacter pylori* of goldthread and/or oubaku.

0005 The stomach and intestinal medicine of this invention is a medicine characterised in that (1) it combines natural drug powder or extract components of goldthread and medicinal or extract components of dried orange peel or (2) it combines natural drug powder or extract components of oubaku with natural drug powder or extract components of dried orange peel or (3) it combines natural drug powder or extract components of goldthread and oubaku and natural drug powder or extract components of dried orange peel. In particular, a combination of natural drug powder or extract components of goldthread and natural drug powder or extract components of dried orange peel is ideal. These natural drug powder or extract components may be used

together in separate formulations or they may be used as a compound formulation. The proportions of the combination of (1) the natural drug powder or extract components of goldthread and/or oubaku and (2) the natural drug powder or extract components of dried orange peel can be selected at discretion, but goldthread and oubaku are extremely bitter and extremely expensive compared with dried orange peel, which is cheap and easy to take. In the stomach and intestinal medicine of this invention, the dosage of goldthread or oubaku can be relatively reduced owing to the multiplying effect through the special combination of medicinal components (see the experimental examples below). If we consider the proportions of the combination of these medicines from this viewpoint, they can be combined in proportions of about 2~200ppw, when converted to the primary drug, desirably about 5~100ppw, when converted to the primary drug, and still more desirably about 10~50ppw, when converted to the primary drug, of dried orange peel to 1ppw, when converted to the primary drug, of the natural drug powder or extract component of goldthread. They can be combined in the proportions of 1~100ppw, when converted to the primary drug, desirably 2~50ppw, when converted to the primary drug, and still more desirably 3~30ppw, when converted to the primary drug, of dried orange peel to 1ppw, when converted to the primary drug, of natural drug powder or extract component of oubaku. About 1~200ppw, when converted to the primary drug, desirably 5~100ppw, when converted to the primary drug, and still more desirably about 10~50ppw, when converted to the primary drug, of dried orange peel can be combined with 1ppw, when converted to the primary drug, of natural drug powder or extract component of both the goldthread and oubaku. Furthermore, the proportions of the combination of goldthread and oubaku at this time should be in the range of 0.2~30ppw, when converted to the primary drug, desirably about 0.5~10ppw, when converted to the primary drug, and still more desirably about 1~3ppw of oubaku to 1ppw, when converted to the primary drug, of the natural drug powder or extract component of goldthread.

0006 It is desirable that at least one type of histamine H_2 receptor antagonist, proton pump inhibitor, stomach mucous membrane protective type of gastritis and digestive ulcer treatment drug, antacid drug and diarrhoea prevention drug should be combined in the stomach and intestinal medicine of this invention. Examples that can be given of

the histamine H_2 receptor antagonist are such ones as cimetidine, ranitidine, famotidine, roxatidine and nizatidine and their pharmacologically permissible salts. One type or more can be selected from these and used. Examples that can be given of pharmacologically permissible salts or derivatives are such ones as ranitidine hydrochloride, and examples of roxatidine derivatives are such ones as roxatidine acetate hydrochloride. Examples that can be given of proton pump inhibitors are such ones as lansoprazole, omeprazole, antoprazole, rabeprazole and reminoprazole and their pharmacologically permissible salts. One or more of these can be selected and used. It is desirable to use lansoprazole, omeprazole or rabeprazole. With these proton pump inhibitors, it is desirable to suppress the gastritis effects by methods such as using them in combination with the antacids shown below or by making an enteric coated formulation or stabilising formulation (for example, a basic inorganic salt of magnesium or calcium).

0007 Examples that can be given of stomach mucous membrane protective type of gastritis and digestive ulcer treatment drugs are such ones as aldioxa, aldioxa.magnesium metasilicate aluminate, sucralfate, proglumide, teprenone, cetraxate hydrochloride, plaunotol, sofalcone, benexate hydrochloride betadesc, irsogladine maleate, rebapimide, ecabeto sodium and poraprezinc. One or more of these can be selected and used. Among these, sucralfate, cetraxate hydrochloride, teprenone or sofalcone can be ideally used. Examples of antacids that can be given are such ones as dry aluminium hydroxide gel, magnesium silicate aluminate, magnesium silicate, synthetic aluminium silicate, synthetic hydrotalcite, magnesium oxide, aluminium magnesium hydroxide, aluminium hydroxide gel, aluminium hydroxide. sodium hydrocarbon coprecipitation product, aluminium hydroxide.magnesium carbonate mixture dry gel, aluminium hydroxide.magnesium carbonate.calcium carbonate coprecipitation product, magnesium hydroxide, sodium hydrocarbon, magnesium carbonate, calcium carbonate sedimentation, magnesium metasilicate aluminate, anhydrous calcium hydrogen phosphate, calcium hydrogen phosphate and such inorganic antacids; amino acid agents such as amino acetate; dihydroxy aluminium aminoacetate; and Turkey-red oil extract. One or more of these can be selected and used. Examples of diarrhoea prevention drugs that can be given are such ones as

bismuth drugs (for example, bismuth hyposalicylate, bismuth hyponitrate, bismuth hypocarbonate and bismuth hypogallate), tannin agents (for example, tannic acid, albumin tannate and methylene thymol tannin) and the like. One or more of these can be selected and used. Among these, bismuth agents that have a particularly effective action against *helicobacter pylori* are desirable.

0008 There may also be added to the stomach and intestinal medicine of this invention, according to requirements, at least one type of natural drug powder or extract component selected from among such things as Areca, Punica granatum, Liquorice root, Cimicifuga rhizome, Artemisiae capillaris herba, Corydalis tuber, Senna, perilla herb, Actium lappa, Salviae miltiorrhizae, Forsythiae fructus, Moutan cortex, Crataegus, Aconitum carmichaeli, Louicwra japonica, Cyperus rhizome, Carthami flos, Lindera strychnifolia, Lotus seed, Rhubarb, Ginger, Sophora root, Aloe, Peony root, Clove, Scutellaria root, Immature orange and Magnolia bark, desirably at least one type of natural drug powder or extract of Ginger, Scutellaria root, Immature orange, Clove, Liquorice root, Magnolia bark or Corydalis tuber.

0009 The natural drug powders and extract components used in this invention are ones that have been used in herbal medicine from olden times. Natural drug powders or extract components obtained according to common usage can be used unchanged. The medicinal powders or extract components can also be used in the form of the normal product on the market or processed products of these. Powders where dried processed products are pulverised still further or dried products in a fine powder state (medicinal dried powder) can be used as the natural drug powder. Furthermore, there is no particular limitation on the form of the extract component from the natural drug and any form such as dry extract powder, extract powder, soft extract, fluid extract and a tincture containing ethanol or ethanol and water can be used. It is desirable to use extract components with a high degree of freedom in their production such as dry extract powder.

0010 The extract component can be obtained by customary methods, for example, by extracting an active component that has an action against *helicobacter pylori* from a

natural drug listed in this invention by an extraction solvent. For example, water, hydrophilic solvents or mixtures of these are frequently used as the extraction solvent. Examples of the said hydrophilic solvent that can be given are alcohols such as methanol, ethanol, propanol, isopropanol, butanol, isobutanol, s-butanol and t-butanol (desirably soluble alcohols that have of the order of 1~3 carbons such as methanol, ethanol, propanol and isopropanol and more desirably ethanol); Cellosolves such as methyl cellosolve and ethyl cellosolve; ketones such as acetone; ethers such as dioxane and tetrahydrofuran; and solvents containing nitrogen such as pyridine, morpholine, acetonitrile, N,N-dimethyl formamide, dimethyl acetoamide and N-methyl pyrrolidone. These hydrophilic solvents may be used singly or as a mixture of two types or more. In order to extract the component that has activity against *helicobacter pylori* efficiently it is desirable to use, for example, the said alcohols or the said mixture solution of alcohols and water as the extraction solvent. If a mixed solvent of water and a hydrophilic solvent is used as the said extraction solvent, the proportions of the water and the hydrophilic solvent in the mixture are, for example, water/hydrophilic solvent = about 95/5~about 5/95 (by weight), desirably water/hydrophilic solvent = about 90/10~about 50/50 (by weight) and particularly desirably about 85/15~about 60/40 (by weight). The extraction process is carried out at a suitable temperature, for example, about 10°C ~ the reflux temperature of the solvent, desirably about 15~70°C or so. Furthermore, cold immersion extraction at room temperature can be done. The extraction liquid extracted by the extraction solvent may be used just as it is as the extraction component or it may be diluted with water or the like or it may be used as a concentrated extract, where the extraction extract has been concentrated. Normally, an additive agent is added as necessary to the extract substance or concentrated extract when the extract liquid has been concentrated and it is used as a dry extract powder that has been processed into a powder by methods such as spray drying and freeze drying.

0011 The amount of the natural drug powder or extract component of goldthread, oubaku and dried orange peel used in the stomach and intestinal medicine of this invention is not particularly restricted provided that it is an effective amount that exercises a bactericidal action against *helicobacter pylori.* When administered to humans, it differs depending upon such things as form, dosage path, treatment subject

and extent and type of symptoms, but, for example, it is about 0.01~10g, desirably about 0.03~6g, when converted to the primary drug, per day for an adult (weight 60kg) for goldthread; about 0.01~20g, desirably about 0.03~10g for oubaku; and about 0.01~50g, desirably about 0.03~10g for dried orange peel. There is no particular restriction on the number of times of dosage. The dosage may be given once per day or divided among several times. Any one type of such things as cimetidine, ranitidine, famotidine, roxatidine and nizatidine and the like are normally used as the histamine H_2 receptor antagonist. The amount of these histamine H_2 receptor antagonists used can be selected and set by the administrator. It is normally desirable to use them so that they are in the usage range that is used for treatment (for, example, about 1~800mg per day for an adult (60kg)). For example, the dose for a day for an adult (60kg) is desirably about 10~800mg for cimetidine, about 5~300mg where the ranitidine is ranitidine chloride, about 1~40mg for famotidine, about 5~150mg where the roxatidine is roxatidine acetate chloride and about 30~300mg for nizatidine. Furthermore, the number of times of dosage and the method can be suitably selected.

0012 An amount of the dose of proton pump inhibitor should be used so as to be within the dosage range used in normal treatment (for example, about 0.01~100mg per day for an adult (60kg)). The amount of the dose can be suitably selected and set by the administrator. For example, the amount per day for an adult (60kg) is desirably about 0.01~30mg for lansoprazole and about 0.01~20mg for omeprazole. Furthermore, the number of doses may be once per day or with one day's dosage divided among 2~3 times, but it is desirable to have a dosage period that does not exceed 8 weeks altogether as a treatment period for stomach ulcers and 6 weeks altogether as a treatment period for duodenal ulcers. Through its combination with the natural drug components where (1) natural drug powder of extract components of goldthread and/or oubaku and (2) natural drug powder or extract components of dried orange peel are combined, a stronger and faster effect is obtained in the treatment and prevention of re-occurrence of stomach and intestinal disorders caused by *helicobacter pylori*. As a result, although there are differences depending on such things as form, dosage path, treatment subject and degree and type of symptoms, a sufficient effect can normally be

obtained with a dosage period of 8 weeks for the treatment of stomach ulcers and 6 weeks for the treatment of duodenal ulcers.

0013 The stomach and mucous membrane protective type of medicines for the treatment of gastritis and digestive ulcers can be suitably selected and set by the administrator from the usage amounts normally used (for example, about 0.01~3600mg per day for an adult (60kg). The number of doses may be set according to the conditions established in the treatment, but, taking into consideration a balance with other components in combination, it is made once per day or divided among 2~4 times as convenient.

0014 Antacids are used in the range of amounts in normal use. One type or more of these antacids may be combined and mixed. For example, the maximum daily usage amount of inorganic antacids is about 1~30g and the minimum usage amount is 1/100 of this, that is to say, about 0.01~0.3g. The daily amount for an adult (60kg) of aminoacetate, which is an amino acid agent, is about 0.01~2g and the daily usage amount for an adult (60kg) of dihydroxyaluminium aminoacetate is about 0.1~10g. The daily usage amount for an adult (60kg) of Turkey-red extract is about 0.1~100mg. The usage amount can be suitably selected and set by the administrator. For the diarrhoea prevention medicine, the daily usage amount for an adult (60kg) is made to be within the usage range normally used, for example, for bismuth agents it is made to be about 0.01~10g and for tannin agents the daily usage amount for an adult (60kg) is made to be about 0.01~10g. The usage amount can be suitably selected and set by the administrator. Besides these histamine H_2 receptor antagonists, proton pump inhibitors, mucous membrane protective type of treatment medicines for gastritis and digestive ulcers, antacids and diarrhoea prevention components, other components that are mixed in as a norm, for example digestives, medicine for internal disorders, pain killers, mucous membrane restorers and dimethyl polysiloxane active components may be combined and mixed in.

0015 The stomach and intestinal medicine of this invention is normally taken by mouth. There is no particular restriction on the type of oral formulation for the said

stomach and intestinal medicine and it may, for example, be tablets, granules, fine grains, pills, capsules, chewable medicine and such individually formed medicines or, for example, syrup, suspensions, emulsions and such liquid formulations. Normal carriers can be used according to the type of formulation in the preparation of these medicines. For example, in the preparation of individually formed formulations the customary components such as starch, milk sugar, sucrose, mannitol, corn starch and such sugars; crystal cellulose, carboxymethyl cellulose, light anhydrous silicic acid and such excipients; polyvinyl alcohol, polyvinyl pyrrolidone, polyvinyl ether, ethyl cellulose, gum arabic, tragacanth, gelatine, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, calcium citrate, dextrin, pectin and such binders; magnesium stearate, calcium stearate, talc, polyethylene glycol, colloidal silica and such lubricants; starch, carboxymethyl cellulose, calcium carboxymethyl cellulose, sodium cross caramelose and such breakdown agents, auxiliary breakdown agents, moisture retention agents or surfactants and the like can be used. In addition, oral administration of the formulation can be made with a coating by known methods with the aim of masking the taste or making it enteric or long lasting. Examples of coatings that can be used are hydroxypropyl methyl cellulose, ethyl cellulose, hydroxymethyl cellulose, hydroxypropyl cellulose, polyoxyethylene glycol, Tween 80, Pluronic F68, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, hydroxymethyl methyl cellulose acetate succinate and Oidragid [translit.] (made by the Romaco, Germany, methacrylic acid-acrylate copolymer) and titanium oxide, red oxide and such colorants. The oral dosage formulations can desirably be made, for example, by the method in Japanese Patent Announcement Hei 3-38247 or a method corresponding to this.

0016 In preparing liquid formulations the normal components can be used, for example, water (including water for injection), ethyl alcohol, ethylene glycol and such solvents; ethanol, polyethylene glycol, propylene glycol, D-mannitol, cholesterol, triethanol amine, sodium carbonate, sodium citrate and such dissolution auxiliaries; suspension agents of hydrophilic macromolecules such as stearyl triethanol amine, sodium lauryl sulphate, lecithin, glycerine monostearate and such surfactants; polyvinyl alcohol, polyvinyl pyrrolidone, sodium carboxymethyl cellulose, methyl cellulose, hydroxymethyl cellulose, hydroxyethyl cellulose and hydroxypropyl cellulose;

phosphates, acetates, carbonates, citrates and such buffer agents; grape sugar, amino acids and the like. According to requirements, preservatives, solubilising agents, emulsifiers, dispersants, thickeners, plasticisers, adsorbents, perfumes, colorants, taste and smell correctors, sweeteners, decay prevention agents, antacids and the like can be used in the said individually formed medicines and liquid medicines.

0017 The stomach and intestinal medicine of this invention can be prepared by customary methods according to the type of formulation such as mixing, kneading, granulation, tablet forming, coating, sterilisation treatment and emulsification. Moreover, with regard to preparation of the formulation, this can be done in conformity with all the provisions for formulations in the Japan Pharmacopeia. The stomach and intestinal medicine of this invention, because it uses natural drug components that have been used for medical use since olden times as its main components, can be administered with safety to mammals including humans without toxicity or side effects. The stomach and intestinal medicine of this invention is effective for the treatment and prophylaxis of all sorts of stomach and intestinal disorders, especially gastritis, stomach ulcers and duodenal ulcers, caused by *helicobacter pylori*. With the stomach and intestinal medicine of this invention, not only a synthetic medicine of (1) natural drug powder or extract component of goldthread and/or oubaku and (2) a natural drug powder or extract component of dried orange peel but also, in conjunction with this, separately prepared effective components may be simultaneously administered or administered at a separate time to the same patient. In addition, at least one type of natural drug powder or extract component or the like besides the proton pump inhibitors, mucous membrane protective type of gastritis and digestive ulcer treatment drugs, antacids, diarrhoea prevention drugs, histamine H_2 receptor antagonists which can be combined with these natural drug powders and extract components and the goldthread, oubaku and dried orange peel may not only be synthesised with them but also used in combination, that is to say, separately formulated effective components may be administered simultaneously or at different times to the same patient.

0018

Form of Embodiment of the Invention

A detailed explanation of this invention is given below, citing practical embodiments.

Practical Embodiments Reference Examples

Preparation of Dry Extract Powder

About 7 times the amount of 30 volume% ethanol aqueous solution (that is, 350ml) was added to 50g of shredded goldthread and it was extracted for 1.5 hours at 50°C while stirring at 30rpm. It was filtered using a standard comb (size 75μm) and the residue was washed in 150ml of 30 volume% ethanol aqueous solution. The recovered filtrate and the wash liquid were combined and suction filtered. The suction filtrate was concentrated at reduced pressure so as to become about 50ml at a temperature below 50°C and a soft extract was obtained. This soft extract was freeze dried for about 24 hours and a dry extract powder was obtained. Dry extract powders of oubaku and dried orange peel were obtained in a similar way.

0019 Test Example

Test of the Suppression of the Propagation of *Helicobacter Pylori* Bacteria

Using the dry extract powder of goldthread, oubaku and dried orange peel obtained in the reference example, the activity through the use of combinations of these against *helicobacter pylori* was measured by the agar-agar flat plate dilution chequerboard method. The dry extract powder was dissolved in sterilised distilled water and in addition a doubly diluted series was further prepared with sterilised distilled water. 2ml test samples of extract combinations in which the various extracts in the dilution series were combined were mixed with 18ml of a culture of Brucella agar with 7% horse blood serum added and a plate for measurement was prepared. Bacteria used for the test were (a) CPY433, TN2 and TN58, which are clinically separate strains, and (b) metronidazole resistant strain NCTC 11916. CPY433 and NCTC 11916 are described in the European Journal of Clinical Microbiology and Infectious Diseases, 14, 391-399, (1995). Furthermore, the TN2 was obtained as 92-244 and the TN58 as 91-196 by cultivating what was allocated from Oita Medical University. Using a cultivation of Brucella broth with 2.5% bovine fetal blood serum added, these test bacteria were shake cultivated for 20 hours at 37°C in a gas pack jar with a CampyPak™ (BBL

Beckton Dickinson Microbiology System) inserted. 5μl of each bacterial liquid adjusted to a concentration in the culture of about 10^6 CFU (colony forming unit)/ml were inoculated onto an agar-agar plate for measurement and cultivated for 4 days at 37°C in a gas pack jar in which a CampyPak and cotton wool containing water were inserted. After cultivation, the growth of the bacteria was observed with the naked eye and the lowest concentration where growth was not observed was made the MIC (minimum growth inhibitory concentration) of the said test extract. The respective FICs (fractional inhibitory concentration) for both extracts in a combination concentration where the strongest interaction was observed were found and the FIC index, that is the sum of the FICs of both extracts, was calculated. The FIC index is explained in Krogstad DJ, Mollering RC: Antimicrobial combinations. In: Lorian V (ed): Antibiotics in Laboratory Medicine. Williams & Wilkins, Baltimore, 1986, P.537-595. Based on this, an FIC index of less than 0.5 was judged to be synergistic, of >0.5~1.0 an arithmetic action, of >1.0~2.0 no interaction (no effect) and >2.0 an antagonistic action.

0020 The results are shown in Table 1. Table 1 shows the FIC values found from the MIC values through a combination of the respective individual MICs and the FIC index consisting of their sum.

Table 1

Anti-bacterial Activity Against *Helicobacter Pylori* by a Natural Drug Extract Combination

Bacteria Strain	FIC (*combined MIC/*single MIC)		FIC index
	Goldthread	Oubaku	
CPY433	0.50 (62.5/125)	0.50 (125/250)	1.00
TN2	0.50 (62.5/125)	0.50 (125/250)	1.00
TN58	0.50 (62.5/125)	0.50 (125/250)	1.00
NCTC 11916	0.50 (62.5/125)	0.50 (125/250)	1.00
	Goldthread	Dried Orange Peel	
CPY433	0.13 (15.6/125)	≤0.25 (500/≥2000)	≤0.38
TN2	0.13 (15.6/125)	≤0.25 (500/≥2000)	≤0.38
TN58	0.13 (15.6/125)	≤0.25 (500/≥2000)	≤0.38
NCTC 11916	0.13 (15.6/125)	≤0.25 (500/≥2000)	≤0.38
	Oubaku	Dried Orange Peel	
CPY433	0.25 (62.5/250)	≤0.25 (500/≥2000)	≤0.50
TN2	0.25 (62.5/250)	≤0.25 (500/≥2000)	≤0.50

TN58	0.25 (62.5/250)	≤0.13 (250/≥2000)	≤0.38
NCTC 11916	0.25 (62.5/250)	≤0.25 (500/≥2000)	≤0.50

*The units of the combined MIC and single MIC are [μg/ml]

The FIC index in the case of the combined goldthread and oubaku is 1.00 and it is judged that this showed an arithmetic action. On the other hand, the FIC index in the case of combined goldthread or oubaku and dried orange peel is ≤0.38~≤0.50 and this was judged to show synergism. In particular, there was marked synergism with the combination of goldthread and dried orange peel. In concrete terms, with goldthread and oubaku there was a strengthening of activity of the order of eightfold with goldthread and fourfold with oubaku through the addition of dried orange peel over the concentration where activity against *helicobacter pylori* was shown by them on their own. Furthermore, with dried orange peel there was a fourfold or more strengthening of activity through adding goldthread or oubaku over the concentration where activity against *helicobacter pylori* was shown by dried orange peel on its own. From this it is judged that there is a clear synergism effect with a combination of goldthread or oubaku and dried orange peel. Furthermore, when the effect in the case where goldthread, oubaku and dried orange peel were combined was studied by the same method as in the above tests, the MIC value in the case of goldthread and oubaku alone fell to ¼ or less through combination with dried orange peel. From the fact that the MIC value of goldthread and oubaku against *helicobacter pylori* fell dramatically when the three drugs were combined, it was judged that, by combining goldthread and oubaku and dried orange peel, the activity against *helicobacter pylori* is greatly strengthened.

0021 Examples of formulation in this invention are set out below in concrete terms but this invention is not limited to these. Also, except where otherwise stated, the amount of admixture of each component shows the daily dose for an adult (60kg) and the formulation is done by normal methods.

Practical Embodiment 1

Prescription	Adult Daily Dose (in 3 packages) [mg]
Goldthread dry extract powder	10

Dried orange peel dry extract powder	320
Cimetidine	300
Sucralfate	1,500
Crystal cellulose	1,200
Starch	450
Hydroxypropyl cellulose	180
Milk sugar	520
Total	4,480

A powder mixture was prepared following the above prescription and a granular medicine was made in accordance with the provisions of the granular medicines section of the regulations for formulations in the Japan Pharmacopeia.

0022

Practical Embodiment 2

Prescription	Adult Daily Dose (in 3 packages) [mg]
Oubaku dry extract powder	50
Dried orange peel dry extract powder	400
Scutellaria root dry extract powder	450
Synthetic hydrotalcite	700
Magnesium oxide	800
Bismuth hypogallate	1,000
Crystal cellulose	900
Starch	600
Hydroxypropyl cellulose	180
Milk sugar	690
Total	5,770

A granular medicine was prepared following the above prescription in accordance with the provisions of the granular medicines section of the regulations for formulations in the Japan Pharmacopeia.

0023

Practical Embodiment 3

Pill Element

Prescription	Adult Daily Dose (in 9 pills) [mg]
Goldthread dry extract powder	10
Oubaku dry extract powder	20
Dried orange peel dry extract powder	300
Ginger dry extract powder	500
Cimetidine	300
Crystal cellulose	444
Starch	295
Hydroxypropyl cellulose	103
Magnesium stearate	20
Milk sugar	700
Sub-total	2,692
Sugar-Coated Pill	
Pill element	2,692
Talc	1,141.1
Gum Arabic	75.3
Titanium oxide	46.3
White sugar	1,104.3
Total	5,059.0

The pill element and sugar-coated pills were made following the above prescription in accordance with the provisions of the pill medicines section of the regulations for formulations in the Japan Pharmacopeia.

0024

Practical Embodiment 4

Prescription	Adult Daily Dose (in 60ml)
Goldthread dry extract powder	10mg
Oubaku dry extract powder	30mg
Dried orange peel dry extract powder	600mg
Magnesium hydroxide	1,000mg
Aluminium hydroxide gel	600mg

Cimetidine	240mg
Refined white sugar	3,000mg
Butyl paraoxybenzoate	7.5mg
Flavour	0.06ml
Sodium hydroxide	suitable amount
Purified water (to make up total)	60ml

The liquid medicine was prepared following the above prescription in accordance with the provisions of the liquid medicines section of the regulations for formulations in the Japan Pharmacopeia. After filtering, it was sterilised and a glass bottle was filled with it.

0025

Effect of the Invention

A strong anti-bacterial activity, especially activity against *helicobacter pylori*, is shown by the stomach and intestinal medicine of this invention. Furthermore, there is no concern about such things as the manifestation of resistant bacteria and side effects like hypersensitivity and diarrhoea that are seen with antibiotics. In addition, it is useful as a medicine, particularly a stomach and intestinal medicine for such things as the prevention, treatment and prevention of re-occurrence of such things as gastritis, stomach ulcers and duodenal ulcers caused by *helicobacter pylori*. Also, as there can be a reduction in the amounts of individual natural powders or extract components used, particularly goldthread and/or oubaku that are expensive and very bitter and unpleasant to take, a formulation that is easy to take can be provided and, in addition to this, there is an economic advantage.